

PATENT SPECIFICATION

809,827



Date of Application and filing Complete Specification: June 23, 1955.

No. 18238/55.

Application made in Switzerland on July 2, 1954.

Complete Specification Published: March 4, 1959.

Index at acceptance:—Classes 2(3), U4(A2:C4); and 81(1), B1Z, B2(B3:C:H:L:N:S:Z).

International Classification:—A61k. C07c.

COMPLETE SPECIFICATION

Hormone Preparations

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to preparations having a content of 3 different testosterone esters, namely testosterone undecylate, testosterone valerate and testosterone propionate. These preparations possess a protracted androgenic effect and are intended for use as medicaments in human and veterinary medicine. Especially valuable are preparations in which the three components, testosterone undecylate, testosterone valerate and testosterone propionate are contained in the approximate proportion of 15:8:2. The content of the testosterone ester mixture in the composition preferably varies between 0.01—50 per cent by weight. In individual doses in order to obtain a therapeutic effect, as for example in single tablet or ampoule, 0.5—500 m.g. of the specified testosterone ester mixture can be present.

The special therapeutic properties of the new hormone preparations can be proved, for example, by experiments on capons. For this purpose, by way of example, individual doses of 2.5 mg. were administered intramuscularly as follows:

1. 1 dose of the testosterone ester mixture according to the present invention, consisting of
35 1.5 mg. of testosterone undecylate
 0.8 mg. of testosterone valerate
 0.2 mg. of testosterone propionate

Total 2.5 mg. mixture

2. 1 dose of 2.5 mg. of testosterone undecylate alone,
40 3. 1 dose of 2.5 mg. of testosterone valerate alone,

[Price 3s. 6d.]

4. 1 dose of 2.5 mg. of testosterone propionate alone.

The silhouette of the comb was measured planimetrically and the growth expressed graphically as a percentage as shown in the accompanying drawing. The individual curves represent average values of experiments with 4—7 capons. It is seen from them that a single dose of the mixture of the three testosterone esters according to this invention (curve 1) has a considerably stronger effect than that of any of the esters alone in the same dosage (curves 2, 3 and 4). A further particular advantage of the new preparations consists in that, compared with the individual esters, they have to some extent a more rapid onset and attainment of the maximum growth and to some extent a more protracted maximum growth. Also on the basis of clinical experiments the new preparations are shown to be a considerable advance as compared with the known medicaments.

The new testosterone ester preparations are prepared by conventional methods, for example with the use of pharmaceutical, organic or inorganic carrier materials such as are suitable for parenteral, enteral or local application. Such substances are concerned as do not react with the testosterone esters, as for example water, vegetable oils, benzyl alcohol, polyethylene glycols, gelatin, lactose, starch, magnesium stearate, talc, Vaseline, cholesterol or other medicament carriers. "Vaseline" is a Registered Trade Mark. Of especial importance are preparations for parenteral administration, preferably solutions, primarily oil solutions, and also suspensions, emulsions or implantates; in a corresponding manner tablets or dragees are produced for enteral application and salves or creams for local application. The preparations can, if desired, be sterilised or subjected to the addition of auxiliary materials such as preserving, stabilising, wetting or emulsifying agents, salts for vasocon-

45

50

55

60

65

70

75

80

85

Price 25^p

Price 75^p

of the osmotic pressure or buffer substances or also other therapeutically valuable materials, for example local anaesthetics or substances having an effect upon the blood vessels.

The following Examples illustrate the invention:

EXAMPLE 1.

OIL AMPOULES

10	Testosterone undecylenate	150 mg.
	Testosterone valerate	80 mg.
	Testosterone propionate	20 mg.
	Benzyl alcohol	40 mg.
	Sesame oil to	1 cc.

15 The production of these oil ampoules can be carried out as follows:

I. The testosterone esters (undecylenate, valerate, propionate) are mixed and finely ground. Then the benzyl alcohol is introduced and the whole heated on the water bath until solution results.

II. The solution I is then diluted with sesame oil, so that 1 cc. of the resulting solution contains exactly 250 mg. of the testosterone esters.

III. The solution is filtered in the customary manner and filled into ampoules; the closed ampoules are heat-sterilised in accordance with the usual directions.

EXAMPLE 2.

CRYSTAL AMPOULES

	Testosterone undecylenate	30.00 mg.
	Testosterone valerate	16.00 mg.
	Testosterone propionate	4.00 mg.
35	Sodium carboxymethylcellulose	5.00 mg.
	Sodium chloride	7.50 mg.
	Sodium phosphate, prim.	2.00 mg.
	Sodium phosphate, sec.	1.00 mg.
	Merthiolate (Registered Trade	

40	Mark)	0.01 mg.
	"Tween" 20 (Registered Trade	
	Mark)	1.00 mg.

Dist. water ad 1.00 cc.

The testosterone esters are ground with the sterilised "Tween" 20 and the suspension agent (see below), added in portions, and then made up to the desired volume with the remainder of the suspension agent. The suspension agent is prepared by bringing the sodium

50 carboxymethylcellulose into solution in the water by way of the swelled condition and dissolving therein the primary and secondary sodium phosphate and also the "Merthiolate" and the sodium chloride. Before use the suspension agent is heat-sterilised. The preparation and filling of the crystal ampoules is

carried out with the observance of aseptic precautions.

EXAMPLE 3.

TABLETS		60
Testosterone undecylenate	15.00 mg.	
Testosterone valerate	8.00 mg.	
Testosterone propionate	2.00 mg.	
<i>p</i> -Stearoylaminophenyl-trimethyl-		
ammonium methyl sulphate	0.10 mg.	65
Lactose	90.00 mg.	
Powdered Sugar	215.00 mg.	
Stearin	3.00 mg.	
Talc	16.90 mg.	
	350.00 mg.	70

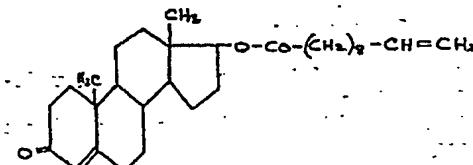
I. The hormones are ground to a homogeneous mixture with a part of the lactose; mixing is then carried out with the remainder of the lactose and the powdered sugar.

II. The *p*-stearoylaminophenyl-trimethyl-ammonium methyl sulphate is dissolved in alcohol and the hormone powder mixture I moistened with the solution, granulated with a little water and dried.

III. The lubricant is added and the whole tableted in the customary manner.

The testosterone esters to be used according to this invention can be produced by known methods. Thus for example, the testosterone undecylenate is obtained in the following manner:

Into a solution, prepared in a dry nitrogen atmosphere, of 28.84 gm. of testosterone in 100 cc. of anhydrous benzene and 30.2 cc. of anhydrous pyridine, 27.0 cc. of undecylenyl chloride are introduced drop-wise within 45 minutes with stirring and external cooling with water at 18-20° C. When the addition is complete, the mixture is stirred for a further 15 hours at room temperature, then poured into 200 cc. of 2N-sulphuric acid and the whole extracted with ether. The ether extract is washed consecutively with 0.5 N-sulphuric acid, water, 0.1 N-caustic soda solution and with water to a neutral reaction, dried with sodium sulphate and evaporated. The solvent-free residue is recrystallised from anhydrous ethanol with cooling in a mixture of ice and common salt. By filtration with suction, washing with 95% ethanol and drying at 25-28° C. under vacuum, pure testosterone undecylenate of the formula:



is obtained in colourless crystals of m.p.
52—53.5° C.

WHAT WE CLAIM IS:—

- 5 1. Hormone preparations with a content of
testosterone undecylenate, testosterone valerate
and testosterone propionate.
- 10 2. Hormone preparations according to claim
1, wherein the relative proportion of testo-
sterone undecylenate, testosterone valerate and
testosterone propionate is approximately
15:8:2.
- 15 3. Hormone preparations according to
claim 1 or 2, having a content of 0.1 to 50
per cent by weight of a mixture of testosterone
undecylenate, testosterone valerate and testo-
sterone propionate.
4. Hormone preparations according to any

one of claims 1—3 having a content of 0.5 to
500 mg. of a mixture of testosterone
undecylenate, testosterone valerate and testo-
sterone propionate in a single tablet or
ampoule.

20

5. Hormone preparations according to any
one of claims 1—4 suitable for parenteral
administration and having a content of testo-
sterone undecylenate, testosterone valerate and
testosterone propionate.

25

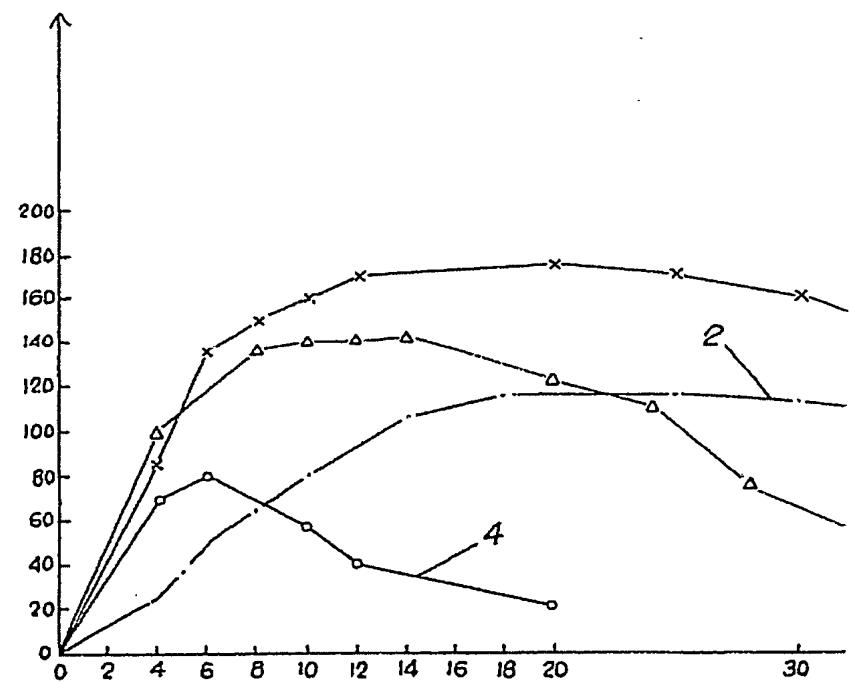
6. Oily solutions according to any one of
claims 1—5 suitable for parenteral admini-
stration and having a content of testosterone
undecylenate, testosterone valerate and
testosterone propionate.

30

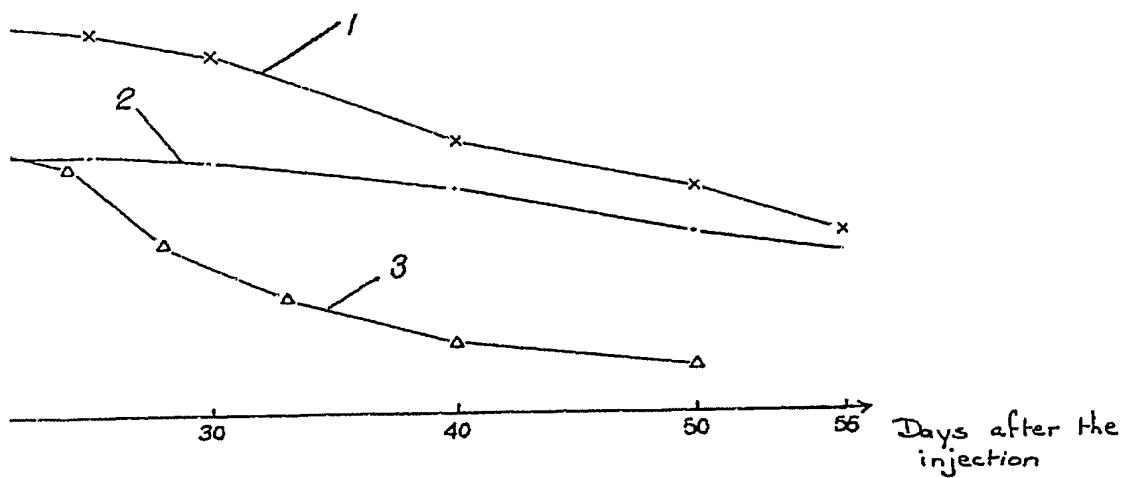
ABEL & IMRAY.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1959.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which
copies may be obtained.

Growth of crest
expressed as a
percentage



809,827 COMPLETE SPECIFICATION
1 SHEET
*This drawing is a reproduction of
the Original on a reduced scale.*



809827 COMPLETE SPECIFICATION
1 SHEET
This drawing is a reproduction of
the Original on a reduced scale.

